Preparation of Crown Compounds Containing Allyloxymethyl or Butenyl Groups for Attachment to Silica Gel or Containing Long Chain Lipophilic Groups for Use in Liquid Membrane Systems

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Several new macrocyclic polyether ligands have been prepared for use in the separation of metal ions from aqueous solutions. Four of the crown ethers reported contain 1,2,4-triazole or 4-pyridone protonionizable subcyclic units and lipophilic groups. The remaining crown ethers are not proton-ionizable but contain alkene groups and were prepared for attachment to silica gel. The crowns were prepared by reacting the appropriate glycols with the appropriate ditosylates or dichloride in the case of the 1,2,4-triazole subcyclic unit. The crowns with proton-ionizable and lipophilic substituents were tested in liquid membrane transport systems and some of the crowns with alloxymethyl or butenyl substituents were attached to silica gel. The log *K* values for the interaction of these silica gel-bound macrocycles with certain metal ions were nearly the same (±10%) as those for the association of the unbound macrocycles with the same metal ions.

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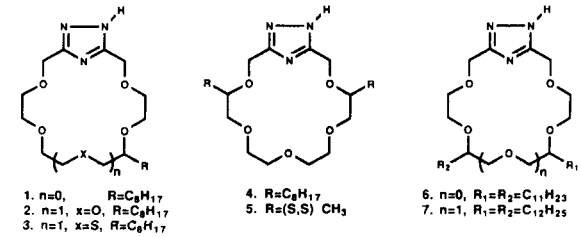
Introduction.

There has been considerable recent interest in the design of macrocyclic compounds for the selective complexation and separation of metal ions. Much of the separation work using macrocycles has involved the extraction of metal ions into organic solvents or the transport of metal ions through liquid membranes. Macrocyclic systems have been studied for the selective extraction and/or transport of lithium [2,3], copper(II) [4], potassium [5], calcium [6], and silver [7] ions to name only a few.

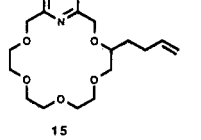
One of the major problems in using the solvent extraction and liquid membrane systems is keeping the macrocyclic molecule in the organic phase. We have prepared many proton-ionizable crowns containing 1*H*-1,2,4-triazole and 4-hydroxypyridine subcyclic units and which also contain lipophilic substituents (**1-5**, **8**, and **9**) [8-11]. Increasing the lipophilicity of the crown ethers is important in keeping the macrocycle in the organic phase of the liquid membrane system used in our transport studies. Macrocycles without lipophilic side groups did not transport metal cations because they were largely distributed to the aqueous phases of the liquid membrane systems [5]. Ligands **1** and **2** with an octyl substituent were good cation transporters in simple membrane systems where the ratio of the volumes of source and receiving aqueous phases to organic phase was about 1:1 [12]. In solid supported liquid membrane systems, the ratio of source and receiving aqueous phases to organic phase is very high and ligand **2** was not retained in the organic layer [13]. Compound **4** with two octyl substituents transported metal cations in the solid supported liquid membrane system but at a lower level. Studies are under way to determine if the lower transport by **4** in solid supported liquid membranes is due to loss of **4** into the aqueous phases or if the two octyl substituents near the triazole ring are causing steric problems [13]. New macrocycles **6** and **7** were synthesized in order to increase the lipophilicity of the macrocycle and give good transport properties by moving the two hydrocarbon chains away from the ionizable triazole moiety. Chiral **5** was not tested for cation transport since it would

Figure 1. Structures of Compounds



1. n=0, R=C_8H_{17}
2. n=1, x=O, R=C_8H_{17}
3. n=1, x=S, R=C_8H_{17}
4. R=C_8H_{17}
5. R=(S,S) CH_3
6. n=0, R_1=R_2=$C_{11}H_{23}$
7. n=1, R_1=R_2=$C_{12}H_{25}$

8. n=0, R_1=H, R_2=C_8H_{17}
9. n=1, R_1=H, R_2=C_8H_{17}
10. n=0, R_1=$CH_2OCH_2CH{=}CH_2$, R_2=H
11. n=1, R_1=H, R_2=$CH_2OCH_2CH{=}CH_2$
12. n=0, R=$CH_2OCH_2CH{=}CH_2$
13. n=1, R=$CH_2CH_2CH{=}CH_2$
14. n=2, R=$CH_2OCH_2CH{=}CH_2$



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not be lipophilic enough to remain in the organic phase of our liquid membrane system. Macrocycles **8** and **9** were lipophilic enough to be useful for the selective transport of silver [7] and potassium [3] ions in a liquid membrane system.

In addition to keeping the crown ether in the organic phase of the transport system, maintaining good crown-cation interactions after substitution with a lipophilic group and recovery of the crown from the liquid membrane system are also major problems. The macrocyclic ligands are difficult and expensive to prepare. Even marginal losses of these materials in a liquid membrane system cannot be tolerated. A new process to attach the crowns to silica gel has been reported [14]. Attachment is through stable covalent bonds so that the crowns are available for complexation with metal and organic cations for an indefinite period of time [14,15]. The attachment process uses hydrosilylation of dimethoxymethylsilane or triethoxysilane and an alkene-containing crown to form the di- or trialkoxy-substituted silane containing the crown. This silane material is then adsorbed onto silica gel and heated to form the silica gel-bound crown [14,15]. Macrocycles **10-15** were prepared for attachment to silica gel.

This paper reports the synthesis of the new macrocycles and gives a summary report of the cation transport properties of **6** and **7**. Macrocycles **12-15** have been attached to silica gel and a preliminary report of the cation complexation properties of these materials is also included in this paper.

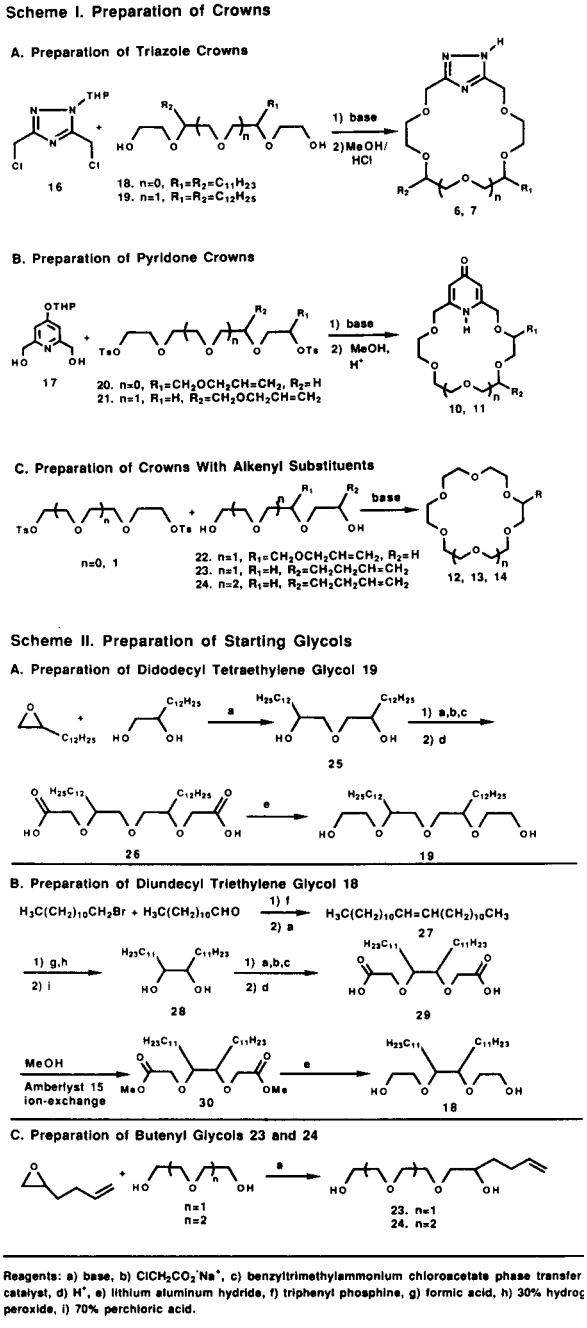
Results and Discussion.

Compounds **6** and **7** were prepared by the reaction of 3,5-*bis*-(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole **16** [9] with the appropriately substituted oligoethylene glycol as shown in Scheme I A. The crude product was reacted with acetic anhydride to acetylate all of the unreacted alcohol functions. All of the acetylated materials were eluted together on silica gel chromatography almost at the solvent front while the crown eluted last. The crown product was deprotected (THP group removed) in cold methanolic hydrogen chloride. When the crown was deprotected before chromatography, very little if any of the pure crown was obtained using silica gel.

Compounds **10** and **11** were prepared by the reaction of 4-(tetrahydro-2-pyranoxy)-2,6-pyridinedimethanol **17** [8] with the ditosylate of the appropriate oligoethylene glycol as shown in Scheme I B. The crude product was deprotected using *p*-toluenesulfonic acid. Contrary to the purification of triazole crowns **6** and **7** mentioned above, pyridono crowns **10** and **11** were purified by column chromatography after the deprotection step.

Macrocycles **12-14** were prepared by the reaction of di-, tri-, or tetraethylene glycol ditosylate with the appropriate

Scheme I. Preparation of Crowns



Scheme II. Preparation of Starting Glycols

Reagents: a) base, b) $ClCH_2CO_2^-Na^+$, c) benzyltrimethylammonium chloroacetate phase transfer catalyst, d) H^+, e) lithium aluminum hydride, f) triphenyl phosphine, g) formic acid, h) 30% hydrogen peroxide, i) 70% perchloric acid.

substituted glycol (as shown in Scheme I C). The crowns were purified by distillation.

Compound **15** was prepared by the reaction of 2,6-pyridinedimethanol and the ditosylate of glycol **24**. In contrast to **6-11**, **15** has no ionizable protons and was easier to purify as well as to attach to silica gel which will be discussed later.

The structures proposed for the new macrocycles were consistent with data obtained from their ir and nmr spectra, molecular weight determinations and combustion analyses. The pyridono crowns **10** and **11** have been shown

to have the 4-pyridone form in solution by the fact that each nmr spectrum exhibited peaks at δ 6.2 indicative of the pyridone C-H hydrogen atoms [8].

Compounds **6-11** and **15** can have positional isomers where one or more of the substituents are on the adjacent carbon atoms. The first step in forming the starting glycols was the reaction of an alkyl-substituted epoxide with an alkoxide to form a di- or triethylene glycol (see Scheme II C for example). The reaction generally occurs on the unsubstituted carbon atom of the epoxide leading to a glycol with a substituent on carbon 1. We suspect that a small percentage of the reaction occurred at the substituted carbon of the epoxide giving a substituent on carbon 2. Jones and his co-workers [16] showed that when dimethyl-substituted tetraethylene glycol was prepared by the same process, about 5% of the methyl groups were on carbon 2. The nmr spectra of the two isomers are virtually the same, therefore, the ratio of the two glycol isomers cannot be determined.

Scheme II A shows the synthesis of starting glycol **19** beginning with commercially available 1,2-epoxytetradecane and an excess of 1,2-tetradecanediol to give **25**. The nmr signals for the hydrogen atoms on carbons 1,2,4 and 5 and the alcoholic hydrogen atoms appeared as a very broad multiplet in the nmr spectrum. The relative ratio was correct even though the individual peaks were not resolved. Diacid **26** was obtained by reacting diol **25** with an excess of the sodium salt of chloroacetic acid in the presence of benzyldimethyl ammonium chloroacetate phase transfer catalyst. The diacid was reduced to diol **19** using lithium aluminum hydride.

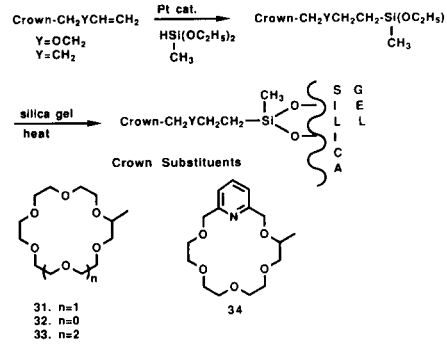
Glycol **18** was prepared by first oxidizing the long-chain alkene to the diol followed by the addition of the sodium salt of chloroacetic acid and reduction (of the dimethyl ester) as shown in Scheme II B. Alkene **27** was prepared by a Wittig reaction as shown. The overall yields of **18** and **19** were about the same.

Compounds **23** and **24** were prepared in a manner similar to **19** as shown in Scheme II C and patterned after the procedure of Okahara and his co-workers for the preparation of allyloxymethyl-substituted triethylene glycol [17]. Ditosylates **20** and **21** were formed by the tosylation of 1-allyloxymethyl-3,6-dioxa-1,8-octanediol [17] and 4-allyloxymethyl-3,6,9-trioxa-1,11-undecanediol [18], respectively.

Satisfactory combustion analyses could not be obtained on the new glycols or ditosylates. Good analyses were obtained on all new crowns which are derivatives of the glycols and ditosylates. The structures proposed for the glycols and ditosylates are consistant with data obtained from their ir and nmr spectra. The glycols all exhibited a broad band at 3500-3400 cm^{-1} in the ir spectra indicative of the hydrogen bonding of their hydroxy groups.

The transport of cations by **6** and **7** in a water-

Scheme III. Preparation of Silica Gel-Bound Compounds



methylene chloride-water bulk liquid membrane system has been determined [12]. Compounds **6** and **7** did not transport metal cations as well as **1** and **2** [12]. While **6** transported Na^+ and K^+ fairly well, it did not transport Rb^+ and Cs^+. Compound **1**, on the other hand, transported Li^+ three times faster than **6** and transported Rb^+ and Cs^+ very well. Compound **7** did not transport Li^+ or Na^+ and transported K^+, Rb^+ and Cs^+ with flux values approximately one-half of those reported for **2**. The decreased transport of cations by **6** and **7** when compared to **1** and **2** could be due to the increased surface activity of these ligands in basic solution, thus making them less available to act as cation carriers [12].

In order to increase the effective use of our crowns in removing cations from aqueous solutions, we have attached crowns **12-15** to silica gel through stable covalent bonds as shown in Scheme III. The silica gel-bound crowns can remove cations from aqueous solutions without the problem of macrocycle distribution to the water phase or the need to recover the expensive crown. The alkene substituent on the crown was reacted with either dimethoxymethylsilane, triethoxysilane, or trichlorosilane in the presence of a platinum catalyst (Scheme III). The crown-silane material was absorbed onto silica gel and heated to form very stable Si-O-Si bonds. The stable hydrocarbon or hydrocarbon-ether linkage allows the use of the crowns for the separation of cations from aqueous solutions without losing the crown into the solution [14,15].

In order for the silica gel bound macrocycles to be effective in selective removal, recovery, and/or separation of specific cations, the properties of the unbound macrocycles must be retained after binding. A comparison of several exemplary cation-macrocycle interaction constants for the analogous bound and unbound macrocycles of this study are given in Table I. It is obvious that the macrocycles attached to silica gel as described in this paper mimic very closely the behavior of the unbound macrocycles.

The removal of metal and organic cations from aqueous

Table I

Comparison of Bound and Analogous Unbound Macrocycle Interaction Constants with Metal Cations

Macrocycles (Scheme III)	Cation	Log K Bound	Log K Unbound [a]
34	H^+	5.1 ± 0.2	5.229 [b]
34	Ag^+	2.7 ± 0.2	5.5 [c]
34	Cu^{2+}	1.8 ± 0.1	4.63 [c]
32	Ag^+	0.90 ± 0.15	0.94
31	Ag^+	1.61 ± 0.09	1.50, 1.60
31	Ba^{2+}	3.56 ± 0.01	3.87
33	Ba^{2+}	2.93 ± 0.09	5.44 [c]

[a] Ref [20]. [b] pKa value for pyridine in water [9]. The pKa value for the unbound macrocycle has not been reported. [c] Log K values measured are in methanol. These values have been shown to be 2-3 log K units higher than the log K values measured in water [20].

solutions is of great interest to us. We are continuing our research on the synthesis of new crowns to attach to silica gel for the selective removal of ions from aqueous solutions [14,15,18].

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Matson FTIR spectrometer. The proton nuclear magnetic resonance (^{1}H nmr) spectra were obtained on JEOL-FX-90Q or Varian Gemini 200 spectrometers using deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass Spectrometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Starting materials were purchased from Aldrich Chemical Co. when available. Starting glycols were prepared as follows.

4,8-Didodecyl-3,6,9-trioxa-1,11-undecanediol (**19**) (Scheme II A).

Compound **25** was first prepared by slowly adding 7.81 g of 85% 1,2-epoxytetradecane in 100 ml of dry dioxane to 27.63 g (0.12 mole) of 1,2-tetradecanediol and 0.2 g of sodium hydride (60% dispersion in mineral oil) in 600 ml of dry dioxane in a 1000 ml 3 neck, round bottom flask equipped with a 125 ml addition funnel, stirrer and a nitrogen gas inlet. The epoxide solution was added dropwise to the stirred refluxing dioxane solution over a period of 3 hours. The mixture was refluxed for an additional 48 hours after which it was cooled to 25° and approximately 6 ml of 3 M sulfuric acid were added with stirring. After a few minutes, an excess of saturated sodium bicarbonate solution was added, the mixture was stirred for 30 minutes, filtered and evaporated. The residue was dissolved in warm ethanol and a white insoluble precipitate was filtered. The ethanol was then evaporated to give 37.96 g of a white material that solidified on standing. Kugelrohr distillation gave 7.70 g (56%) of **25** as a yellow liquid that solidified on standing, mp 78-79°; ^{1}H nmr: δ 3.4-3.8 (m, 8 H), 1.26 (s, 44 H), 0.90 (t, 6 H). This material was used in the next step to prepare **26**.

Glycol **25** (7.44 g, 0.017 mole), 4.0 g (0.034 mole) of chloroacetic acid, sodium salt and 10 mole% of benzyltrimethylammonium chloroacetate phase transfer catalyst were added to 500 ml of dry THF in a 1000 ml, 3 neck round bottom flask equipped with a condenser, stirrer and a nitrogen gas inlet. Potassium t-butoxide (4.6 g) in 200 ml of dry THF was added dropwise to the refluxing mixture. After refluxing for 30 hours, the reaction mixture was cooled to room temperature and 10 ml of concentrated hydrochloric acid was added. The mixture was evaporated to dryness leaving an off-white waxy residue. Concentrated hydrochloric acid (10 ml) in 200 ml of water was added to the residue and after standing at room temperature for a few minutes, the solid residue turned into an oil. The aqueous mixture was extracted 3 times with 100 ml portions of methylene chloride. Compound **25** as a yellow oil (9.1 g, 97%) was obtained after the organic phases were dried over magnesium sulfate and evaporated. The yellow oil solidified on standing. Product **26** was used in the next step to prepare **19** without further purification.

Diacid **26** (9.0 g, 0.016 mole) in 125 ml of anhydrous ether was added dropwise over a period of 2 hours to a stirring suspension of 1.40 g of lithium aluminum hydride in 400 ml of anhydrous ether in a 1000 ml, 3 neck round bottom flask equipped with an addition funnel, nitrogen gas inlet, magnetic stirrer, and condenser. After the addition was completed, the mixture was refluxed for 24 hours. The mixture was then cooled and several drops of water were added with stirring followed by approximately 20 ml of 10% aqueous sodium hydroxide solution. The mixture was filtered and the ether phase was removed. The remaining aqueous phase was extracted 3 times with 200 ml portions of ethyl ether. The combined organic phases were dried over magnesium sulfate and evaporated to leave 7.88 g of a yellow oil. The oil was flash chromatographed on 80 g of 200-400 mesh silica gel using ethyl acetate/hexane:9/1 as eluant to give **19** as a soft white waxy solid; ir (neat): 3407 cm^{-1}; ^{1}H nmr: δ 4.28 (b, 2 H), 3.28-3.88 (m, 14 H), 1.26 (s, 44 H), 0.88 (t, 6 H). The product was used to prepare **7**, which gave a satisfactory elemental analysis.

4,5-Diundecyl-3,6-dioxa-1,9-octanediol (**18**) (Scheme II B).

Compound **27** was first prepared by combining 26.28 g (0.10 mole) of triphenylphosphine and 24.97 g (0.10 mole) of dodecyl bromide in 300 ml of dry DMF (dried over 4 Å sieves and run through an alumina column) in a 1000 ml round bottom flask. The mixture was heated at 120° for 2 days. The DMF was evaporated and the glassy residue was washed with hot hexane. The phosphonium salt in 160 ml of dry THF and 18.4 g (0.10 mole) of dodecanal in 120 ml of dry THF were simultaneously dripped into 300 ml of dry refluxing THF containing 12.4 g (0.11 mole) of potassium t-butoxide in a 3-necked round bottom flask over a 2-hour period. The resulting solution was refluxed overnight. The THF was evaporated and the residue was passed through a pad of silica gel eluting with hexane. The hexane was evaporated and the residue was dissolved in 200 ml of ether. The ether solution was washed with 200 ml of brine solution. The brine solution was washed with two 200 ml portions of ether. The combined organic layers were dried over magnesium sulfate, filtered and evporated. The residue was filtered through a thick pad of silica gel eluting with hexane to obtain 30.88 g (92%) of **27** as a clear oil; ^{1}H nmr: δ 5.36 (m, 2 H), 1.28 (s, 40 H), 0.88 (t, 6 H). This material was used in the next step to prepare **28**.

Alkene **27** (29.75 g, 0.088 mole) was added dropwise to a stirred solution of 53 ml of 88% formic acid and 13 ml of 30% hydrogen

peroxide in a 250 ml, 3 neck round bottom flask which was cooled in an ice bath. When a white waxy solid appeared, the addition was stopped, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature and then warmed to 45° before addition was continued. The temperature remained around 45° without heating during the completion of the addition. The reaction was stirred overnight at room temperature. A white gelatinous solid formed which was dissolved in hexane and the hexane solution was separated. The hexane was evaporated leaving an oil and a small amount of water. Sodium hydroxide (7.1 g) dissolved in 30 ml of water was added to the oil and the mixture was warmed. The aqueous solution was then extracted with three 200 ml portions of ether. The combined organic phases were dried over magnesium sulfate, filtered, and evaporated. After checking the ir and nmr spectra to be sure that the epoxide was formed, the white solid was dissolved in 200 ml of THF and 34 g of 70% perchloric acid were added. The mixture was stirred for 3 days at 25° at which time the solvent was removed. Water (200 ml) and 300 ml of ether were added to the remaining white solid. The aqueous phase was extracted 2 more times with 300 ml portions of ether. The combined organic phases were then dried over magnesium sulfate, filtered, and evaporated to leave 26.82 g (82%) of **28** as an off white waxy solid; ^{1}H nmr: δ 3.39 (m, 2 H), 2.80 (b, 2 H), 1.23 (s, 40 H), 0.87 (t, 6 H). This material was used in the formation of **29**.

Diacid **29** was prepared as described above for **26** using 26.56 g (0.072 mole) of the glycol **28**, 16.69 g (0.143 mole) of the sodium salt of chloroacetic acid, 10 mole% of benzyltrimethylammonium chloroacetate phase transfer catalyst, and 20.91 g (0.186 mole) of potassium *t*-butoxide. After refluxing for 30 hours and cooling to 25°, the mixture was acidified with aqueous hydrochloric acid and then evaporated to dryness. The residue was dissolved in ether and aqueous brine solution. The aqueous phase was extracted twice with 300 ml portions of ether. The combined ether layers were dried over magnesium sulfate, filtered, and evaporated to obtain 33.93 g (97%) of **29** as a yellow oil; ^{1}H nmr: δ 8.7 (b, 2 H), 4.02 (s, 4 H), 3.42 (b, 2 H), 1.26 (s, 40 H), 0.87 (t, 6 H). This material was used to prepare **30**.

Diacid **29** (33.0 g, 0.068 mole) was dissolved in 350 ml of methanol and 20 g of Amberlyst 15 ion exchange resin were added. The mixture was allowed to stir at reflux for 30 hours. After the reaction was cooled to 25°, the solvent was evaporated and the residue dissolved in methylene chloride. The Amberlyst resin was filtered and the solvent was evaporated to give 31.42 g of a yellow oil. The oil was flash chromatographed on 310 g of 200-400 mesh silica gel using 350 ml of hexane then 4% acetone in hexane as eluants. Product **30** was obtained as a clear oil (23.18 g, 66%) and used to prepare **18**.

Compound **18** was prepared as described above for **19** using 18.21 g (0.035 mole) of **30** and 2.0 g of 95+ % lithium aluminum hydride. Compound **18** was obtained as a yellow oil which was flash chromatographed on 150 g of 200-400 mesh silica gel using 300 ml of hexane and then 15% acetone in hexane as eluents to give 10.59 g (66%) of a slightly yellow oil; ir (neat): 3415 cm^{-1}; ^{1}H nmr: δ 3.69 (s, 8 H), 3.40 (m, 2 H), 3.16 (b, 2 H), 1.26 (s, 40 H), 0.88 (t, 6 H). This compound was used to prepare **6**, which gave a satisfactory elemental analysis.

1-(3-Butenyl)-3,6-dioxa-1,8-octanediol **23** (Scheme II C).

1,2-Epoxy-5-hexene (9.8 g, 0.1 mole) was added dropwise over a 1-hour period to a stirred solution of 1.12 g (0.02 mole) of potassium hydroxide dissolved in 33 g (0.3 mole) of hot diethylene glycol. The solution was stirred for an additional hour and then cooled to 25°. The solution was neutralized with dilute sulfuric acid and the solvent was evaporated. The resulting liquid was distilled twice using a vigreux column at 118-120°/0.01 mm Hg to obtain 15 g (75%) of **23**; ir (neat): 3420 cm^{-1}; ^{1}H nmr: δ 6.0-6.2 (m, 3 H), 3.6 (m, 13 H), 2.15 (m, 2 H), 1.5 (m, 2 H). This material was used to prepare crown **12**, which gave a satisfactory elemental analysis.

1-(3-Butenyl)-3,6,9-trioxaundecanediol Ditosylate of Diol **24**.

The ditosylate of **24** was prepared from the corresponding diol which in turn was prepared as described above for compound **23** using triethylene glycol and 1,2-epoxy-5-hexene. The crude diol was distilled at 140-142°/0.01 mm Hg to obtain purified **24** in a 69% yield. Diol **24** was then dissolved in pyridine at about -5°. Tosyl chloride was also dissolved in pyridine and added very slowly to the cold stirring diol solution. After 5 hours of stirring at -5°, the solution was poured onto ice along with concentrated hydrochloric acid. The resulting oil was separated and the residue was extracted twice with methylene chloride. The oil was combined with the methylene chloride phases and dried over magnesium sulfate. After filtration and evaporation, the residue was chromatographed on silica gel with methylene chloride as the eluent to obtain the ditosylate of **24** in a 48% yield; ^{1}H nmr: δ 7.8 (d, 4 H), 7.3 (d, 4 H), 5.8 (m, 1 H), 4.8 (m, 2 H), 4.65 (q, 1 H), 4.2 (m, 2 H), 3.6 (m, 12 H), 2.45 (s, 3 H), 2.2 (s, 3 H), 1.9 (m, 4 H). This material was used to prepare crown **15**, which gave a satisfactory elemental analysis.

Preparation of Macrocyclic Compounds.

7,8-Diundecyl-3,6,9,12-tetraoxa-15,16,17-triazabicyclo[12.2.1]-heptadeca-1(16),14-diene (**6**) (Scheme I A).

3,5-*Bis*-(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**16**) (2.18 g, 8.72 mmoles) in 125 ml of dry THF and glycol **18** (4.0 g, 8.72 mmoles) and 2.49 g (22 mmoles) of potassium *t*-butoxide in 125 ml of dry THF were added slowly and simultaneously over a 1.5-hour period to 250 ml of dry THF in an oven dried 1000 ml, 3 neck, round bottom flask equipped with two 125 ml addition funnels, a condenser, and a nitrogen gas inlet. The mixture was refluxed for an additional 48 hours. The cooled reaction mixture was filtered and evaporated. The residue was dissolved in 200 ml of methylene chloride and extracted several times with 100 ml portions of aqueous brine solution. The organic layer was dried over magnesium sulfate, filtered, and evaporated to leave 7.29 g of a rust-colored oil. The oil was dissolved in 200 ml of pyridine and acetylated with 1.6 ml of acetic anhydride using 4-*N*,*N*-dimethylaminopyridine as a catalyst. The mixture was stirred at 25° for 3 hours and then about 2 ml of ethanol were added and the mixture was stirred for ½ hour. The solvent was evaporated and the residue was dissolved in 100 ml of toluene. The toluene was evaporated to remove water. The residue was chromatographed on 75 g of 200-400 mesh silica gel using ethyl acetate/hexane:1/1 followed by ethyl acetate/hexane:7/3 followed by ethyl acetate/hexane:9/1 as eluents to obtain 1.83 g of a slightly yellow oil. The THP blocking group was removed by stirring the oil in about 50 ml of methanolic hydrogen chloride for several hours at 25°. The methanol was evaporated and the residue was neutralized with 75 ml of aqueous sodium bicarbonate solution. The product was extracted with three 100 ml portions of methylene chloride. The

organic layer was washed with 50 ml of saturated brine and dried over magnesium sulfate to give 1.26 g (26%) of a gummy solid, mp 70°; ^{1}H nmr: δ 4.72 (s, 4 H), 3.74 (s, 8 H), 3.3 (m, 2 H), 1.25 (s, 40 H), 0.87 (t, 6 H).

Anal. Calcd. for $C_{32}H_{61}N_3O_4$: C, 69.64; H, 11.14; N, 7.61; M$^+$, 551.8. Found: C, 69.72; H, 11.10; N, 7.53; M$^+$, 551.

7,11-Didodecyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo-[15.2.1]eicosa-1(19),17-diene (**7**) (Scheme I A).

Compound **7** was prepared as described above for **6** using 1.35 g (5.27 mmoles) of **16**, 2.8 g (5.27 mmoles) of **19**, and 1.40 g (12.5 mmoles) of potassium *t*-butoxide. A light yellow oil (4.25 g) was obtained and acetylated. The resulting material was chromatographed on 65 g of 200-400 mesh silica gel using ethyl acetate/-hexane:1/1 followed by ethyl acetate/hexane:7/3 as eluents to obtain 1.65 g of a slightly yellow oil. The oil was deprotected to give 1.58 g (48%) of a slightly yellow oil that solidified on standing, mp 77.5-79°; ^{1}H nmr: δ 4.79 (s, 4 H), 3.67 (m, 14 H), 1.25 (s, 44 H), 0.88 (t, 6 H).

Anal. Calcd. for $C_{36}H_{69}N_3O_5$: C, 69.30; H, 11.14; M$^+$ 623.95. Found: C, 69.34; H, 11.34; M$^+$ 623.97.

4-Allyloxymethyl-3,6,9,12-tetraoxa-18-azabicyclo[12.3.1]octadeca-14,17-diene-16(18*H*)-one (**10**) (Scheme I B).

Sodium metal (0.5 g, 22 mmoles) was dissolved in 300 ml of dry *t*-butyl alcohol after which 2.6 g (11 mmoles) of **17** were added to the solution. Compound **20** (5.7 g, 18 mmoles) in 100 ml of dry dioxane was slowly dropped into the mixture over a 5-hour period at 60°. The mixture was then refluxed for 24 hours. The cooled reaction mixture was filtered and washed with dichloromethane. The solvent was evaporated and the residue was dissolved in 100 ml of methanol. *p*-Toluenesulfonic acid monohydrate (3 g) was added to the solution and the mixture was refluxed for 24 hours. Potassium hydroxide was added to the cooled solution until it was neutralized. The solvent was then evaporated and the residue was chromatographed on alumina using toluene/ethanol:10/1 as eluent to give 1.43 g (38%) of **10** as a viscous yellow oil; ir (neat): 3170, 2950, 1640, 1100 cm^{-1}; ^{1}H nmr: δ 9.8 (b, 1 H), 6.18 (s, 2 H), 5.9-5.2 (m, 3 H), 4.7-4.4 (m, 5 H), 4.05-3.4 (m, 14 H).

Anal. Calcd. for $C_{17}H_{25}NO_6$; C, 60.16; H, 7.42, M$^+$ 340. Found: C, 59.96; H, 7.37, M$^+$ 340.

7-Allyloxymethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]-heneicosa-17,20-diene-19(21*H*)-one (**11**).

Potassium metal (2 g, 50 mmoles) was dissolved in 300 ml of dry *t*-butyl alcohol and the solution was warmed to 60°. Compound **17** (5.4 g, 24 mmoles) in 100 ml of dry dioxane and compound **21** (13.5 g, 24 mmoles) in 100 ml of dry dioxane were each added simultaneously to the basic solution over a period of 3 hours. The mixture was refluxed for an additional 5 hours. The mixture was then treated as above for **10** to yield 3.17 g (35%) of **11** as a solid, mp 77°; ^{1}H nmr: δ 10.0 (b, 1 H), 6.2 (s, 2 H), 5.9 (m, 1 H), 5.1 (m, 2 H), 4.45 (m, 4 H), 4.0-3.4 (m, 19 H).

Anal. Calcd. for $C_{19}H_{29}NO_7$: C, 59.52; H, 7.62, M$^+$ 383. Found: C, 59.54; H, 7.58, M$^+$ 383.

1-Allyloxymethyl-3,6,9,12,15-pentaoxacyclopentadecane (**12**) (Scheme I C).

Diethylene glycol ditosylate (21.7 g, 52 mmoles) in 250 ml of dry dioxane and 11.5 g (52 mmoles) of **22** [19] in 250 ml of dry dioxane were simultaneously dripped into a mixture of 4.3 g (0.107 mole) of potassium metal dissolved in 500 ml of dry *t*-butyl alcohol in a 2000 ml three neck round bottom flask equipped with two addition funnels, condenser, and nitrogen gas inlet at 60°. After the addition was completed, the mixture was refluxed for 48 hours. The mixture was then cooled to 25°, filtered, and evaporated. The resulting brown residue was dissolved in 500 ml of water and extracted with two 250 ml portions of hexane. The aqueous layer was extracted with three 250 ml portions of methylene chloride. The methylene chloride was evaporated and, to the brown residue, was added 15.0 g of sodium bicarbonate. The mixture was distilled using a Kugelrohr apparatus to give 2.0 g (13%) of **12** as an oil. The ir and ^{1}H nmr spectral data for **12** agreed with that reported by Okahara and his co-workers [19].

1-(3-Butenyl)-3,6,9,12,15,18-hexaoxacyclooctadecane (**13**) (Scheme I C).

Triethylene glycol ditosylate (50.6 g, 0.1 mole) in 400 ml of dry dioxane was added to a refluxing mixture of 10 g (0.256 mole) of potassium metal dissolved in 1.4 l of dry *t*-butyl alcohol and 22.8 g (0.11 mole) of **23** over a 5-hour period. This mixture was treated as above for the preparation of **12** to give an oil. The oil was purified by short path distillation at 135-137°/0.08 mm Hg to yield 15 g (47%) of **13** as a clear oil; ir (neat): 3500, 2930, 1100 cm^{-1}; ^{1}H nmr: δ 5.9 (m, 1 H), 5.0 (m, 2 H), 3.6 (m, 23 H), 2.15 (m, 2 H), 1.5 (m, 2 H).

Anal. Calcd. for $C_{16}H_{30}O_6 \cdot \frac{1}{4}H_2O$: C, 59.51; H, 9.52; M$^+$ 318. Found: C, 59.55; H, 9.62; M$^+$ 318.

1-Allyloxymethyl-3,6,9,12,15,18,21-heptaoxacycloheneicosane (**14**) (Scheme I C).

Compound **14** was prepared as above for **12** using 40.0 g (0.080 mole) of tetraethylene glycol ditosylate, 17.53 g (0.080 mole) of **23** and 6.85 g (0.18 mole) of potassium metal to give 9.0 g (30%) of a clear oil; ^{1}H nmr: δ 5.85 (m, 1 H), 5.25 (m, 2 H), 4.0 (d, 3 H), 3.85-3.45 (m, 28 H).

Anal. Calcd. for $C_{18}H_{34}O_8$: C, 57.12; H, 9.06; M$^+$ 378. Found: C, 57.03; H, 9.14; M$^+$ 378.

4-(3-Butenyl)-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**15**).

To a stirred mixture of 4.5 g (0.115 mole) of potassium metal dissolved in 800 ml of dry *t*-butyl alcohol and 7.0 g (0.05 mole) of 2,6-pyridinedimethanol were added 27.8 g (0.05 mole) of the ditosylate of **24** in 200 ml of dry dioxane over a period of 3 hours at 60°. The resulting mixture was stirred under reflux for 24 hours then cooled and filtered. The solid residue was washed with methylene chloride and toluene. The combined filtrate was evaporated and the residue was chromatographed on an alumina column using toluene/ethanol:150/1 as the eluent to give 5.0 g (29%) of **15**; ^{1}H nmr: δ 6.40 (m, 3 H), 5.80 (m, 1 H), 5.0 (m, 4 H), 4.48 (s, 2 H), 3.6 (m, 15 H), 2.15 (m, 2 H), 1.6 (m, 2 H).

Anal. Calcd. for $C_{19}H_{29}NO_5 \cdot \frac{1}{4}H_2O$: C, 64.11; H, 8.36; M$^+$ 351. Found: C, 64.21; H, 8.21; M$^+$ 351.

4-(18-Crown-6-yl)butyl-Substituted Silica Gel (**31**) (Scheme III).

Butenyl-18-crown-6 (**13**) (0.5 g, 1.6 mmoles) was reacted with 0.21 g (1.6 mmoles) of dimethoxymethylsilane at 85° in benzene with chloroplatinic acid as the catalyst. After 24 hours, the nmr spectrum showed that there was no remaining alkene. The solvent was removed under vacuum to yield 0.7 g of an oil. The oil was adsorbed onto 7.0 g of silica gel by suspending the silica gel

in a solvent, adding the crown, and then removing the solvent. The resulting material was then heated under vacuum in a Kugelrohr apparatus at 120° to form the bond to the silica gel. The final silica gel was washed successively with toluene, ethanol and methanol.

3-(15-Crown-5-yl)propoxymethyl-Substituted Silica Gel (**32**) (Scheme III).

Compound **32** was prepared as described for **31** using 1.95 g (6.7 mmole) of **12**, and 0.9 g of dimethoxymethyl silane.

3-(21-Crown-7-yl)propoxymethyl-Substituted Silica Gel (**33**) (Scheme III).

Compound **33** was prepared as described above for **31** using 2.0 g (5.3 mmole) of **14** and 1.0 g of triethoxysilane.

3-(Pyridino-18-crown-6-yl)butyl-Substituted Silica Gel (**34**) (Scheme III).

Compound **15** (1.5 g, 4.1 mmoles) was hydrosilylated onto 1.0 g of trichlorosilane in a small bomb to prevent the escape of the trichlorosilane. The silylated crown was then attached to silica gel by suspending 10 g of silica gel in toluene in a round bottom flask equipped with a mechanical stirrer, condenser, and addition funnel. The crown-silane, dissolved in toluene, was slowly dripped into the refluxing suspension. The mixture was slowly stirred and refluxed for 24 hours. The silica gel was filtered and washed successively with toluene, ethanol and methanol.

Determination of Log *K* Values for Silica Gel-Bound Macrocycles.

The determination of bound macrocycle-cation interaction constants was performed as described elsewhere [14].

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